PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/01613	International filing date *(day/month/year)* 15.04.2003	Priority date *(day/month/year)* 15.04.2002
International Patent Classification (IPC) or both national classification and IPC A61K45/06		
Applicant UNIVERSITY OF LIVERPOOL		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.10.2003	21.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Greif, G Telephone No. +49 89 2399-8659

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/01613

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-40 as originally filed

Claims, Numbers

1-19 received on 30.04.2004 with letter of 30.04.2004

Drawings, Sheets

1/13-13/13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-19 (all in parts)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-19 (all in parts)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions: See separate sheet

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-19 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of functional features or parameters, i.e. "agent that attenuates Topoisomerase I activity" and "agent that inhibits Heat Shock Protein 90", which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.
Although the application gives methods to identify suitable compounds having those functions, and although such methods are also known in the art, the present wording of the claims would also include compounds that have not yet been invented, or that are not known to have this function. The present claims thus lack clarity in the sense of Art. 6 EPC.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Under Rule 66.1(e) PCT, a preliminary examination is not carried out on matter which has not been searched. Therefore, the preliminary examination has been carried out on the parts of claims 1-19 that have been covered by the search, i.e. the parts referring to specific compounds.

2. Reference is made to the following document/s/:

D1: M.E.CARDENAS E.A.: "Antifungal activities of antineoplastic agents: Saccharomyces cerevisiae as a model system to study drug action" CLINICAL MICROBIOLOGY REVIEWS, vol. 12, no. 4, 1999, pages 1-56, XP002952701

D2: Y.XIANG, S.ZENG: "The anti-proliferative effect of inhibitor of telomerase on cultured retinal pigment epithelial cells" JOURNAL OF TOGJI MEDICAL UNIVERSITY, vol. 21, no. 2, 2001, pages 174-176, XP008018763

D3: NECKERS L: HSP90 inhibitors as novel cancer chemotherapeutic agents. Trends in Molecular Medicine, 2002, Vol. 8 (4), pp. S55-S61

D4: TEICHER B A et al: Addition of a topoisomerase I inhibitor to tromodailty therapy in a murine tumor, J. Cancer Res. Clin. Oncol., 1993, Vol. 119, pp. 645-651

D5: GOLD DV et al, Successful treatment of pancreatic cancer by combined

gemcitabine and low dose radioimmunotherapy with 90Y labeled PAM4 antibody. Proceedings of the American Association for Cancer Research, March 2002, Vol. 43, pp. 395f

D6: Fukuda M et al, Synergism betwen Cisplatin and Topoisomerase I inhibitors NB-506 and SN-38 in human small cell lung cancer cells. Cancer Research, 1996, Vol. 56, pp. 789-793.

Documents D3-D6 were not cited in the search report.

3. Novelty

D1 discloses topoisomerase inhibitors (p.1-5) and HSP90 inhibitors (p.23-25), being antineoplastic agent, in the context of an antifungal activity. Since a combination of the two classes of drugs is not suggested by D1 for chemotherapy, claims 1-19, to the extent that they refer to specific compounds that have been covered by the search, are novel over D1.

4. Inventive Step

D3-D6 all refer to the combination of various classes of compounds in the field of chemotherapy. It is a priory not considered to be inventive to combine compounds from two different classes of chemotherapeutic agents, especially since their use in the field is known (see D1, D2).

As far as the synergistic effects are concerned that the applicant shows for the combination of a) irinotecan and geldanamycin or b) irinotecan and radicicol or c) topotecan and geldanamycin, the applicant is reminded that synergistic effects are not predictable and are, per definition, unexpected. Therefore, although the applicant does show a synergistic effect for a specific combinations, this does not imply that other claimed combination for which no synergy has been shown, especially any combination of unspecified compounds defined by mechanisms of actions, would also have such an effect.

Since there is no claim that discloses a specific combination of active compounds for which a synergistic effect has been show, claims 1-19 are not considered to be inventive.

5. Industrial applicability

For the assessment of the present claims 1-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of

claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLAIMS

1. A use of a first agent that attenuates Topoisomerase I (Topo I) activity and a second agent that inhibits Heat Shock Protein 90 (HSP90) activity in the manufacture of a medicament for contemporaneous or sequential administration in chemotherapy.

2. The use according to claim 1 wherein the first agent is a compound selected from:

(i) compounds that bind to Topo I and inhibit its activity;

(ii) compounds which prevent the transcription, translation or expression of Topo I;

(iii) compounds which inhibit release of Topo I from intracellular stores; and

(iv) compounds which increase the rate of degradation of Topo I.

3. The use according to claim 1 or 2 wherein the first agent is a cleavable-complex inhibitor.

4. The use according to claim 1 or 2 wherein the first agent is Camptothecin.

5. The use according to claim 1 or 2 wherein the first agent is Topotecan.

6. The use according to claim 1 or 2 wherein the first agent is Irinotecan.

7. The use according to claim 1 or 2 wherein the first agent is Camptostar (CPT-11).

8. The use according to claim 1 or 2 wherein the first agent is Gemcitabine.

9. The use according to any preceding claim wherein the second agent is a compound selected from:

(i) compounds that bind to HSP 90 and inhibit its activity;

(ii) compounds which prevent the transcription, translation or expression of HSP 90;

(iii) compounds which inhibit release of HSP 90 from intracellular stores; and

(iv) compounds which increase the rate of degradation of HSP 90.

10. The use according to claim 9 wherein the second agent is Geldanamycin.

11. The use according to claim 10 wherein the second agent is 17-Allylamino,17-demethoxygeldanamycin (17AAG) or CNF-101.

12. The use according to claim 9 wherein the second agent is Radicicol.

13. The use according to any preceding claim wherein the chemotherapy is for cancer treatment.

14. The use according to claim 13 for the treatment of solid tumours.

15. The use according to claim 14 for the treatment of bowel cancer, small cell and non-small cell lung cancer, head and neck cancer, breast cancer, bladder cancer or malignant melanoma.

16. The use according to claim 15 for the treatment of paediatric tumours.

17. The use according to claim 13 or 16 for the treatment of neuroblastoma, leukaemias and lymphomas.

18. The use according to any one of claims 1 - 12 wherein the chemotherapy is for:

antibacterial treatments;

antifungal treatments;

antiparasitic treatments;

the treatment of AIDS/HIV;

the treatment of multiple sclerosis; or

the killing and inhibition of proliferation of any organism.

19. The use according to any preceding claim wherein the chemotherapy is for prophylactic treatment.